

REMARKS

Claims 1-90 are pending in the application. The examiner has withdrawn claims 81-90. Applicants amend claims 1-8, 10-11, 13, 15-25, 27-29, 31-38, 41, 43-44, 49-59, 66-67, 70-77, and 79-80 for clarity and as suggested by the examiner. Therefore, no new matter has been added. The office action is discussed below:

Election/Restrictions

In response to the office action mailed December 7, 2005 (Paper No./Mail Date 20051129), applicants hereby elect with traverse Group I (Claims 1-80) as set forth by the examiner for prosecution in the subject application. Applicants, of course, reserve the right to file one or more divisional applications covering the subject matter of the non-elected claims.

Applicants traverse the restriction requirement on the grounds that the examiner has not demonstrated the requisite "serious burden" needed to justify a restriction requirement. See MPEP § 803(B) at 800-4 (Rev. 3, August 2005). Given that the examiner is likely to conduct searches in related classes, applicants submit that that there would be no serious burden to examine all of the claims, or at least the claims of Group I and Group II as set forth by the examiner.

Claim Rejections under 35 USC § 112

On pages 4 to 13 of the office action, the examiner has rejected claims 1-80 under USC §112, second paragraph, and alleged as being indefinite for various reasons. Without acquiescing to the rejection, in order to expedite the prosecution, applicants amend claims 1-8, 10-11, 13, 15-25, 27-29, 31-38, 41, 43-44, 49-59, 66-67, 70-77 and 79-80 for clarity and as suggested by the examiner. Withdrawal of the rejection is requested.

Claim Rejections under 35 USC § 103

On pages 13 to 19 of the office action, the examiner has rejected: claims 1-4, 57, 62, 63, 70, 71, and 76-80 under USC §103(a), allegedly as being unpatentable over Naughton et al. (5,962,325) in view of Bessea et al.; claims 56-61, 64, 65, 66, 69 and 72-75; claims 56-61, 64, 65, 66, 69 and 72-75 further in view of Vacanti et al. (6,455,311 B1); claims 66 and 67 further in view of Lyons et al. or Nusgens et al.; claims 5-56 further in view of Ruberti et al.; and claims 5-56 further in view of Lee et al. (WO 00/34442), and Agarwal et al.).

The examiner believes that Naughton discloses: methods of culturing stromal cells on a three-dimensional matrix (see paragraph bridging cols. 10 and 11) to from stromal tissue; during culturing, extracellular matrix protein including collagen is produced in the matrix (see col. 6, lines 10-21); the three-dimensional matrix can be coated with collagen (see col. 11, line 12); and cells cultured on the matrix can be chondrocytes, fibroblasts and/or cells capable or producing collagen type II and other collagen types, and proteoglycans which are typically produced in cartilaginous tissues (see col. 6, lines 15-20, and col 14, lines 20-50).

The examiner also believes that Bessea discloses: methods of producing ordered collagen matrices for three-dimensional cell culture and the ordered collagen matrices contain fibrillar organization close to that *in vivo*. Thus, the examiner believes that it would have been obvious to use the three-dimensional matrix of Naughton in combination with the ordered three-dimensional collagen matrix of Bessea to obtain property of the collagen matrix having a fibrillar organization close to that *in vivo*.

Applicants respectfully disagree because the examiner has failed to establish a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness, at least two criteria must be met. First, there must be a reasonable motivation or suggestion to make the proposed combination or modification of the references. Further, "the teaching or suggestion to

make the claimed combination must be found in the prior art, and not based on the applicant's disclosure." MPEP 2142 (Rev. 2, May 2004), discussing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). In addition, the combined, or modified, references must teach or suggest all claim limitations.

When an examiner alleges a *prima facie* case of obviousness, such an allegation can be overcome by showing that (i) there are elements not contained in the references or within the general skill in the art, (ii) the combination is improper (for example, there is a teaching away or no reasonable expectation of success) and/or (iii) objective indicia of patentability exist (for example, unexpected results). See *U.S. v. Adams*, 383 U.S. 39, 51-52 (1966); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve*, 230 USPQ 416, 419-20 (Fed. Cir. 1986). Applicants submit that the rejections do not meet this test.

Applicants provide following explanations in order to assist the examiner is distinguishing the cited arts from the claimed inventions and also submit arguments to overcome the 35 USC § 103 rejection:

It is not possible to arrive at the claimed invention using the scaffolding disclosed by Naughton et al.

Naughton et al. discloses use of stromal cells and grows them on a three-dimensional framework. Naughton methods used scaffolds (see col. 6, lines 8-20, for example), which can be a number of materials, and are designed to purely support the stromal cells as they grow and generate connective tissue proteins. The majority of the materials proposed for this scaffold are artificial although collagen, in the form of sponges, braids or woven threads, is suggested. Therefore, Naughton's method of culturing stromal cells differ from the instant method and do not generate a support structure like the instant invention, which is highly ordered and resembles very closely the structure of the target connective tissue or stroma. In addition, activated fibroblasts

of the instant template would continue to produce this highly ordered structure. Thus, the resulting structure would have the same physical properties and structure as the native connective tissue, such as the stroma. This result would be impossible to achieve with the scaffolding proposed by Naughton et al. Therefore, use of any matrix in combination of Naughton's method would not result into the claimed invention and therefore Naughton teaches away from the present invention. See *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994) (stating, "in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant."). In view of the case law, the rejection should be withdrawn.

The Besseau et al. process would result in weakly aligned polymers

The Besseau describes adding cells to an ordered matrix, which is governed purely by concentration of the solution and the resulting liquid crystalline behavior, i.e., self-assembly of the polymerizing collagen, and is thus only weakly aligned over long distances. The claimed method produces a template that has long range orientation and spatial organization that is governed by the shearing mechanism, and the solution conditions. Thus, it can generate structures that are much closer to the natural ECM in areas such as tendon or stroma, and does so through a different orientation mechanism that will result in structures even closer to the *in vivo* situation. The combined methods of making these highly ordered structures, and the addition of cells and tension results in an ECM that is truly comparable to the natural target ECM, and particularly to tissue where spacing and fibrillar organization is highly critical, such as in the stroma. In addition, the claimed method obtains the orientation through the motion of the fluid, and can thus be used at a range of concentrations significantly below those quoted by Besseau et al. (see claim 36, for example). Therefore, there is no reasonable expectation of success to arrive at the claimed invention by combining Besseau et al. and Naughton et al. methods.

Besides, as discussed above, use of any matrix in combination of Naughton's method would not result into the claimed invention. Therefore, there is no motivation with reasonable expectation of success to combine the use of Naughton's matrix in combination with the matrix of Bessea to arrive at the claimed inventions. Also, there is no motivation with reasonable expectation of success to use Naughton's method of culturing stromal cells in the matrix of Bessea to arrive at the claimed inventions.

Withdrawal of the obviousness rejection is respectfully requested.

The Vacanti process can not generate structured tissue of the tendon or stroma

Vacanti discloses building a multi-laminar structure to generate tissues that require vascularization but the target tissue is not the highly ordered. In contrast, structured tissue of the tendon or stroma can be generated by the claimed methods. Vacanti uses molds to define the macroscopic structure on the length scale of the vascularization desired, and then seeds cells onto the mold to define the vascularized tissue. However, there is no mechanism in this process for controlling the growth of the collagen (or other material) in such a way as to ensure alignment. These molded layers (and the resulting multi-layer laminates) would therefore work well as liver replacement but would not be considered as a structural extra-cellular matrix according to the instant invention.

As discussed above, Bessea in combination with Naughton's method would not result into the claimed invention. See *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994) (stating, "in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant."). Vacanti does not rectify the deficiencies of the combination of Naughton and Bessea, therefore, further combination of Vacanti would not make the claimed invention obvious.

Regarding Lee et al., applicants point out that Lee et al. describes alignment of cells using flow. Thus, it is not the same as aligning growing polymer fibrils and will not result in the claimed nanostructure.

Applicants also point out that Agarwal et al. uses simple shear flow which aligns rod-like molecules in the direction of the flow. However, this alignment is an average alignment and in fact the molecules are likely to be aligned, but tumbling, in the flow direction. There is no obvious method of using the large volume reaction described where the molecules are aligned on average of Agarwal et al. to generate a thin highly aligned polymeric film. By using shear flow and confining the polymerizing molecules in a thin fluid film, the claimed methods can forceably align the molecules into a highly ordered structure and make them grow in a single plane.

In sum, applicants state that the cited arts makes use of seeding cells onto a suitable template, activating them for growth, and stacking the resulting layers to produce *in vivo*-like tissue constructs. However, the claimed methods provide highly ordered tissue layers and the methods of stacking is also novel and non-obvious, because no known method can generate layers as thin and as highly aligned layers as the claimed invention. Consequently, the claimed methods are highly novel and non-obvious approach of producing tissue analogs that are structurally, biologically and functionally capable of replacing natural materials. The high degree of order and control of fibril spacing and size that is critical for a fully functional stroma can only be obtained through the claimed methods.


As discussed above, Bessea in combination with Naughton's method would not result into the claimed invention. Applicants also submit that, Lyons et al, Nusgens et al, Ruberti et al., Lee et al., and / or Agarwal et al. do not rectify the deficiencies of the combination of Naughton et and Bessea et al., therefore, further combination with any of Lyons et al, Nusgens et al, Ruberti et al., Lee et al., and / or Agarwal et al. would not make the claimed invention obvious.

Applicants therefore request withdrawal of the obviousness rejection.

REQUEST

Applicants submit that the claims 1-80 are in condition for allowance and respectfully request favorable consideration to that effect. The examiner is invited to contact the undersigned at (202) 912-2000 should there be any questions.

Respectfully submitted,



John P. Isacson
Registration No. 33,715

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Date

HELLER EHRMAN LLP
1717 Rhode Island Avenue, NW
Washington, DC 20036
Telephone: (202) 912-2000
Facsimile: (202) 912-2020
Customer No. 26633